Accepted Manuscript

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PII: S1389-9457(15)00037-4
DOI: http://dx.doi.org/doi: 10.1016/j.sleep.2015.01.004
Reference: SLEEP 2641

To appear in: *Sleep Medicine*

Received date: 7-9-2014
Revised date: 4-12-2014
Accepted date: 5-1-2015

Please cite this article as: Katja Linda Waller, Erik Lykke Mortensen, Kirsten Avlund, Merete Osler, Birgitte Fagerlund, Martin Lauritzen, Poul Jennum, Subjective sleep quality and daytime sleepiness in late midlife and their association with age-related changes in cognition, *Sleep Medicine* (2015), http://dx.doi.org/doi: 10.1016/j.sleep.2015.01.004.

Subjective sleep quality and daytime sleepiness in late midlife and their association with age-related changes in cognition

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Conflicts of interest: None of the authors reports any conflict of interests.

Number of words: 5315

Author contributions:
Katja Linda Waller: Study conception and design, acquisition of data, statistical analysis, interpretation of data, and drafting of manuscript, main author.
Martin Lauritzen (ML) and Poul Jennum (PJ): Study conception and design, acquisition of data, critical revision of the manuscript.
Erik Lykke Mortensen (EM): Study conception and design, acquisition of data, statistical analysis and interpretation of data, critical revision of the manuscript.
Merete Osler (MO): Study conception and design, acquisition of data, and statistical analysis and interpretation of data, critical revision of the manuscript.
Kirsten Avlund (KA) and Birgitte Fagerlund (BF): Study conception and design, acquisition of data, critical revision of the manuscript.

Keywords: Sleep quality, elderly people, cognitive decline, cognition

Our co-author, Kirsten Avlund, died on 1st September 2013. She made a significant contribution to this paper, and was fully aware of its content before her death.

Highlights;

(Subjective sleep quality and daytime sleepiness in late midlife and their association with age-related changes in cognition)

- We examined the association between sleep and cognitive function.
- Sleep quality was evaluated with Pittsburgh Sleep Quality Index and sleepiness with Epworth Sleepiness Scale.
- We found evidence for lower self-rated sleep quality in men with cognitive decline.
- We suggest that self-rated sleep quality may be early markers of cognitive decline in midlife.

Abstract

In an increasingly aged population, sleep disturbances and neurodegenerative disorders have become a major public health concern. Poor sleep quality and cognitive changes are complex health problems in ageing populations that are likely to be associated with increased frailty, morbidity and mortality and to be potential risk factors for further cognitive impairment. We aimed to evaluate whether sleep quality, excessive daytime sleepiness and other sleep-related symptoms may be considered as early predictors of cognitive impairment.

Study Objectives: To examine whether subjective sleep quality and daytime sleepiness are associated with cognition in middle-aged males and to determine whether self-rated sleep characteristics are related to cognitive performance.

Participants: We studied 189 healthy males born in 1953 and recruited from the Metropolit Cohort. Based on previous cognitive assessments in young adulthood and late midlife, the participants were selected for the study as cognitively improved (N = 97) or cognitively impaired (N = 92).

Methods: The Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS) measured subjective sleep quality and daytime sleepiness. Depressive symptoms were determined using BDI-II. A comprehensive neuropsychological battery including subtests from the Cambridge

Neuropsychological Test Automated Battery (CANTAB) and MMSE, ACE, Digit, Trail Making A and B, and 15 word pairs were administered to confirm group differences in cognitive functioning at the time when sleep data were collected.

Results: Overall, 41% of the sample exhibited poor sleep quality (global PSQI score ≥ 5) and 15% experienced excessive daytime sleepiness (ESS ≥ 10). Compared with cognitively improved males, the cognitively impaired group reported significantly lower subjective sleep quality (5.40 ± 3.81 *vs.* 4.39 ± 2.40, p = 0.03). The mean ESS score was 5.84 ± 3.42 and 6.51 ± 3.15 in the cognitively impaired and the cognitively improved groups (p > 0.05). There were few correlations between sleep parameters and cognitive test performance in the combined sample, and these were all weak.

Conclusion: Self-reported poor sleep quality was related to cognitive changes, whereas daytime sleepiness was not. Our results suggest that sleep quality may be an early marker of cognitive decline in midlife. More research to clarify the underlying mechanisms of these associations is needed.

1. Introduction

Advancing age is accompanied by a decline in sleep quality and cognitive abilities. In an increasingly aged population, sleep disturbances and neurodegenerative disorders have become a major public health concern. Sleep disturbances are common symptoms in the elderly and the prevalence of sleep problems increases with advancing age. As people age they appear to report prolonged sleep onset, disrupted sleep maintenance, increased likelihood of nocturnal awakenings, earlier waking, increased daytime sleepiness, and daytime napping [1-3]. The subjective meaning of good sleep quality, a widely used concept in the literature, mainly involves sleep continuity, feeling rested and daytime alertness [4;5], factors that may be considered markers of well-being and successful aging [6]. Nearly half of older adults report poor sleep [1], but sleep problems are less prevalent in healthy adults [6-11]. Thus, despite the well established normal alterations in sleep physiology with age [12-14], dissatisfaction with sleep and decline in sleep quality are not an inevitable part of aging *per se* [15]. Rather, sleep in the elderly is affected by underlying physical or mental illness, primary sleep disorders or changes in circadian rhythms [2;3;7;16-18]. Inadequate or poor sleep is associated with decreased quality of life, increased consumption of sleep medications, depressed mood, anxiety, daytime sleepiness and increased risk of frailty and mortality [17;19-24]. Moreover, growing evidence suggests that neurodegenerative diseases may affect sleep beyond the normal aging process [25]. Sleep-wake and circadian disruptions, insomnia and daytime sleepiness are common symptoms in neurodegenerative disorders, possibly due to a common mechanistic origin [25-29]. Impaired sleep may precede cognitive symptoms [23], accompany mild cognitive impairment (MCI) [30] and increase in magnitude with the advancing severity of a dementia disease [31;32]. In patients with MCI, quantitative and qualitative sleep disturbances are more prevalent than in healthy agers and may be considered to be intermediate between the conditions in normal aging and dementia [30;33].

Most findings in non-demented elderly people suggest an association between perceived sleep pattern and cognitive performance, yet it remains unknown whether impaired sleep may hasten or aggravate age-related cognitive decline or vice versa. Moreover, age-related changes in cognition [34] and sleep pattern are substantially heterogeneous, and could be related to changes in circadian and homeostatic processes [35]. However, the underlying mechanisms of these differences remain poorly understood. To date, we have relatively few longitudinal data about the role of qualitative sleep measures as potential precursors of future cognitive decline, and results are

somewhat inconsistent. Mixed findings may reflect differences in samples and measurement characteristics, and perhaps a selective vulnerability to the negative effects of age-related sleep changes [36]. Given that subtle cognitive alterations may occur years before clinical cognitive impairment [37;38] and that sleep quality and quantity may be associated with an increased risk of cognitive decline, it is worth studying this issue further in healthy aged subjects.

Here, based on survey of a community-dwelling sample of healthy middle-aged males, we addressed the association between cognitive changes and sleep pattern using subjective aspects of sleep derived from the Epworth Sleepiness Scale and the Pittsburgh Sleep Quality Index. We hypothesized that cognitively impaired subjects would show lower sleep quality and greater daytime sleepiness than cognitively improved subjects. Moreover, we sought to determine the extent to which qualitative sleep measures are associated with cognitive performance at follow-up.

2. Methods

2.1 Subjects

The current sleep study was based on a subpopulation of 189 middle-aged Danish males recruited from the Metropolit cohort, which comprises 11,532 males born in 1953 in the Copenhagen Metropolitan area. The 189 males in the study sample were selected from 1985 members of the Metropolit cohort who had participated in a follow-up study in 2009-2011 as part of the establishment of the Copenhagen Aging and Midlife Biobank (CAMB) [39]. A more detailed description of the original Metropolit cohort has been presented elsewhere [40]. Only data relevant to the present study will be described here.

Draft board intelligence scores of the members of the Metropolit Cohort had previously been collected [40]. The draft intelligence test is the Børge Priens Prøve (BPP), which has a correlation coefficient of 0.82 with the Wechsler Intelligence Scale [41]. As part of the CAMB midlife data collection, three subtests of the Intelligent Structure Test (I-S-T 2000R) were administered. The BPP and the IST 2000 R are highly correlated (0.70) with a retest interval of almost 40 years in the large sample from which the extreme residuals were selected [42]. A regression model was developed to predict the expected level of midlife cognitive performance from the military draft board intelligence scores. Based on this model the participants of the present study were selected according to the estimated change in intelligence from young adulthood to midlife. Based on the residuals from this regression model we identified 249 individuals who performed substantially better (standardized residuals ranging from 2.80 to 0.96) and 302 individuals who performed

substantially worse (standardized residuals ranging from -3.20 to -0.99) in the midlife cognitive test than expected from their military draft board intelligence score. Of the 551 potential participants, 37 were excluded for various reasons (three potential participants died within the study period), and the remaining 514 individuals were invited to participate in a clinical follow-up study. 102 (41%) of the individuals with substantially better than expected midlife cognitive scores and 105 (34.8%) of those with substantially worse than expected cognitive scores participated in the clinical study.

In summary, between 2010 and 2012 we invited a total of 551 subjects to take part in studies of MRI, oral health, sleep and cognition. A more detailed description of the cohort and the study selection has been presented elsewhere [43].

The final sample of males completing the sleep examinations included 92 subjects classified as cognitively impaired and 97 participants classified as cognitively improved. Any history of neurological or psychiatric disorder, major depressive illness (within the past ten years) or abuse of alcohol or drugs prompted a subject's exclusion from participation. There were no inclusion or exclusion criteria based on sleep.

Data collection involved sleep questionnaires, overnight polysomnographic recordings, a structured clinical interview covering sociodemographic characteristics, medical and family histories and standard laboratory blood tests. A physical examination included measurements of blood pressure, waist, weight and height. Cognition was evaluated by a comprehensive battery of neuropsychological tests.

Investigators were blinded to group status during data collection. After recruitment, written and verbal information were given about the procedures. All subjects provided their written consent before data collection. The study design was approved by the local scientific ethics committee (no. H-3-2010-016).

2.2 Sleep and mood questionnaires

Participants completed a number of self-administrated standardized questionnaires to assess sleep and mood, including the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS), and Beck's Depression Inventory (BDI-II). The reliability and validity of these sleep questionnaires has generally been reported as being acceptable [8;44-48].

Subjective sleep quality was assessed with the PSQI [8]. This 19-item questionnaire measures sleep condition retrospectively over a one-month period, and consists of seven

components; subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances (including items such as having difficulty breathing and feeling pain), use of sleeping medication and daytime dysfunction. The individual component scores are summed to give a global PSQI score. The higher the score, the lower the sleep quality, and a global PSQI score > 5 indicates poor sleep quality. Habitual sleep duration and sleep latency were collected at the same time as part of the PSQI.

The general level of perceived daytime sleepiness was measured using the ESS [44]. Responders are asked to rate on a scale from 0-3 how likely they would be to doze off or fall asleep in each of eight situations. The summed scores vary from 0-24, with a score ≥ 10 indicating excessive daytime sleepiness (EDS).

Depressive symptoms were evaluated using the BDI-II [46;48]. This self-rating scale is a 21-item questionnaire designed to assess depressive symptom severity and cover cognitive, affective and somatic aspects of depression. BDI-II yields a sum score range from 0 to 63, which are categorized as "minimal" (0–13), "mild" (14–19), "moderate" (20–28) or "severe" (29–63) depression.

2.3 Neuropsychological tests

Cognitive performance was assessed with a neuropsychological test battery including seven selected subtests of from the Cambridge Neuropsychological Test Automated Battery (CANTAB) and six traditional paper-and-pencil tests.

The CANTAB, which has been widely used in clinical trials and research, consists of modules for assessing a range of cognitive functions, including memory and attention, planning and reasoning abilities, psychomotor and motor speed and temporal and frontal dysfunctions. The test battery was selected to assess functions that have been shown to be sensitive to both normal aging effects and to the neuropathology of MCI and dementia. All tests of CANTAB are standardized, computerized and presented on a touch screen. We administered the following tests: 1) Visual memory: delayed matching to sample (DMS), paired associates learning (PAL), pattern recognition memory (PRM), and spatial recognition memory (SRM) tests; and 2) Spatial planning: Stockings of Cambridge (SOC); and 3) Sustained attention: rapid visual information processing (RVP); and 4) Response latency and movement time: reaction time (RTI). A more complete description of the test modules may be found on Cambridge Cognition's website: http://www.cantab.com.

The following paper-and-pencil tests were also administered: The Mini-Mental State Examination (MMSE), Addenbrooke's Cognitive Examination (ACE), Trail Making Test A and B (TMT A and B), verbal paired associative learning test, and Symbol digit modality test (SDMT).

Global mental ability was assessed with Mini Mental Status Examination [49] and Addenbrooke's Cognitive Examination. The latter incorporates the MMSE, expands memory, language, and visuospatial components, and adds tests of verbal fluency [50]. Tests of cognitive processing speed, attention and flexibility included Trail Making A and B [51] and the Symbol digit modality test [52].

Verbal memory was assessed with a Danish version of the verbal paired associative learning test [53]. Cognition was evaluated in the morning by trained staff during a structured face-to-face interview lasting for about 2 h in a quiet room at the Department of the Clinical Neurophysiology at Glostrup Hospital. 90% of the participants were tested within 1 week of the day of their sleep examination, and in most cases on the same day.

Statistical analysis

All statistical analyses were performed using SPSS (version 19.0). Continuous variables were summarized as mean ± standard deviation and categorical variables as percentages. For continuous variables, normality was tested for using the Kolmogorov-Smirnov test. Group differences were then examined using unpaired t-tests for normally distributed variables, or Mann-Whitney U tests for non-normal data. Chi-square tests were used to examine differences between the study groups for categorical variables. Results were considered statistically significant for values of $p < 0.05$. In order to evaluate the association between cognitive performance and sleep, Pearson's correlations were calculated between each cognitive test score and sleep measure.

3. Results

3.1 Sample characteristics

The analyzed sample included 189 Caucasian males (mean age 57.92 ± 0.69 years). Clinical and demographic characteristics of the subgroups are presented in Table 1. The cognitively impaired group spent less time in education than the cognitively improved group ($p < 0.01$). Moreover, in cognitively impaired participants there was a trend towards an increased frequency of musculoskeletal illness, most commonly osteoarthritis, rheumatoid arthritis and arthritis urica.

Cognitively impaired participants were significantly more likely to report use of daily medications ($p < 0.01$). 19 subjects (10%) reported some former episode of minor depressive or anxiety disorder. Medication use is shown in Table 2. Only six subjects (3%) of the whole sample were currently using antidepressant, anxiolytic or antiepileptic medications. The subjects with a prescription of selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), benzodiazepines or antiepileptic drugs were all in the cognitively impaired group ($p < 0.01$). Due to the very infrequent use of psychotropic medications and the low frequency of depressed mood in the sample, medication use and depression were not included as covariates in further analyses. No significant group differences were found in any other demographic, clinical or health parameter (i.e., age, BMI, blood pressure, waist circumference, smoking and alcohol-drinking habits or self-reported health conditions).

3.2 Cognitive tests

A previous principal component analysis of the 16 test scores from the CANTAB and paper-and-pencil tests showed that the most meaningful varimax rotated factor solution was obtained when eight components were retained. These components explained 73% of the variance and on the basis of this analysis the following mean standardized test scores were calculated: (1) overall mean of all test scores, (2) mean of MMSE and ACE, (3) mean of the two Trail Making scores and SDMT, (4) mean of the word pair scores,) (5) mean of the two DMS scores, (6) mean of the PAL scores, (7) mean of SRM and SOC, and finally (8) mean of RTI and RVP A. Table 3 presents the mean test scores in the groups with cognitive decline and cognitive improvement. All means were standardized to a mean of 0, a standard deviation of 1, with higher scores indicating better performance.

Table 3 shows that the two groups attained almost identical mean BPP scores in young adulthood while dramatically different late midlife scores were obtained on the I-S-T 2000R. Furthermore, the table shows significant group differences on the overall test mean and on all 7 means of correlated test scores. For the overall test mean, the difference between the two groups corresponds to more than 1 SD, and thus the comprehensive clinical neuropsychological test battery confirmed the large differences in cognitive performance between the two groups.

3.3 Sleep and mood measurements

ESS, BDI-II and PSQI scores including seven PSQI components were compared between groups (Table 4). The global PSQI score was significantly higher in the cognitively impaired males than the cognitively improved males (5.29 ± 3.70 *vs.* 4.31 ± 2.32; p = 0.03). About 40% of the participants in the whole sample had poor self-rated sleep quality, defined as PSQI > 5. 16% of the participants had an ESS score ≥ 10, indicating daytime sleepiness. There was a non-significant trend towards increased sleep latency in participants with impaired cognition. Mean self-rated sleep duration and sleep latency for the whole sample were 6.6 ± 1.14 h and 14 ± 17 min, respectively. When using a cut-off value of ≥ 14 on the BDI-11 scale (Beck 1996), 7 (3.7%) individuals reported symptoms indicating depressed mood (p = 0.6). None of the other sleep characteristics (i.e., ESS, sleep latency, sleep duration) and none of the seven PSQI subcomponents showed significant group differences. The polysomnography results will be reported elsewhere.

3.4 Correlations between sleep measures and cognitive tests

We conducted correlation analyses to examine the relationship between cognitive test scores and sleep measures in the combined sample of 189 participants. In general, this revealed some statistically significant, but weak correlations. The partial correlations adjusted for BPP between sleep measures and cognitive test scores are presented in Table 5.

Global sleep quality was significantly correlated with the overall test mean (r = -0.30, p < 0.01) and significantly but weakly with the mean derived from MMSE/ACE (r = -0.19, p < 0.01). Sleep latency showed a weak negative but significant correlation with all cognitive measures except for the mean word pair scores. Daytime sleepiness, total sleep duration and depression score showed no correlation with any of the cognitive test measures.

4. Discussion

In the present study we examined whether sleep self-reports, assessed with the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale, were related to cognitive changes and performance in healthy middle-aged community-dwelling males. The most interesting finding was that changes in cognition were associated with decreased sleep quality, suggesting that subjective sleep quality may be an early sign of cognitive decline. Groups did not differ with respect to reports of daytime sleepiness, sleep duration or sleep latencies. Although cognitively impaired subjects were more likely to have increased sleep latency, this association was not statistically significant. The

correlation analysis based on the total sample showed that sleep latency was significantly associated with most of the cognitive tests, and global sleep quality was associated with the overall test mean and global cognition. No significant correlations were seen between ESS score, sleep duration and cognitive measures. Another important finding was that more than half of the whole sample reported good sleep quality and the vast majority were not sleepy.

Several cross-sectional studies have reported associations between qualitative [36;54-69] and quantitative [56;70-75] sleep measures and impaired cognitive function in elderly individuals, particularly in the domains of executive function, memory and attention. In addition, self-reported short or long sleep duration [54;57;61;62;65;67;71;76] or changes in sleep quantity [66;77] have all been found to be associated with poorer cognitive function in cross-sectional studies [57;61;62;65;71;76;78] and an increased risk of cognitive decline longitudinally. [66;67;77;79;80].

Even fewer studies have used data collected on multiple occasions to address longitudinal associations between cognition and self-rated sleep symptoms [67;80-86] or quantitative sleep measures [73-75;87-89] in healthy non-demented elderly people, and the findings of these studies have been inconsistent.

A population-based study of subjects aged 65 years or more showed greater cognitive decline over 1 year in men (but not in women) reporting poor sleep quality (measured by the PSQI), short sleep duration and a low level of sleep efficiency at baseline [80]. Cricco et al. [83] found that chronic insomnia was associated with the development of cognitive decline over three years in non-depressed elderly males, and depressed women only, which was confirmed and extended in a longer follow-up study by Osorio [81]. Tworogger found no relationship between subjective sleep complaints, snoring and sleep duration and cognition in older women using a two-year follow-up [61]. However, in the cross-sectional part of the study they found that sleep disturbances and short sleep duration related to impaired cognition. Another large prospective cohort study [90] reported that sleep complaints in those aged 50 years or more were associated with the development of greater cognitive decline over a three-year period, compared with those who did not report sleep problems at baseline. This association was confounded by depressive symptoms. Unlike insomnia symptoms [61;82;84;85], excessive daytime sleepiness (EDS) has been found to be a reliable marker of future cognitive decline over periods of three [85], four [91], eight [84] and ten [82] years. However, levels of daytime sleepiness are not always elevated in MCI subjects compared

with healthy agers [92-94]. Moreover, sleep quality, measured with the PSQI, has been found to be the same in individuals with MCI and the non-demented elderly [95], and even more prevalent in non-demented than demented individuals [96], suggesting that the PSQI is a suboptimal tool for individuals with significant cognitive decline.

The discrepant findings obtained in the above studies may partly be explained by differences in study design, the populations included, age, follow-up time and lack of control for confounders. Some studies have relied on a somewhat limited cognitive evaluation (global cognition) at baseline and follow-up [67;80;88;90]. Lastly, it is possible that different sleep measures may address different aspects of sleep health. Discrepancies between subjective and objective sleep quality and quantity are common in the general adult population [15;58;97-99] and sleep misperception may be intensified by cognitive deficits or insomnia [93;100]. Thus, results from studies involving the objective assessment of sleep may not be entirely comparable to those using self-rated measures of sleep.

A potential relationship between sleep abnormalities and cognitive decline (and potential later development of cognitive impairment) is likely to be complex and to involve multiple factors. Specific sleep abnormalities have been identified, such as REM sleep behavior disorder, that may precede development of Parkinson's disease and other synucleinopathies [101]. However, cognitive impairment may be due to many factors such as taupathies, vascular lesions, and depression, amongst others. We doubt that any single specific measure would encompass the entire range of cognitive impairment including MCI.A major issue not addressed by this study is whether the association between poor sleep and cognitive decline is causal or if some unknown factor is responsible for the conjoint decline. Sleep quality could be a consequence of poor cognitive functioning or a cause of cognitive decline, but poor sleep quality and cognitive decline may be associated because they are influenced by one or more common factors.

The current study raises the possibility that cognitive decline may increase the risk of poor sleep. The psychological consequences of cognitive decline could lead to poor quality sleep. Thus, cognitive decline may be associated with stress and worry about the future, and with behavioral changes related to lack of personal control, all of which may increase the likelihood of poor sleep quality. Behavioral factors such as negative emotions, feelings of distress, worries and changes in self-perception of sleep [93;95] may be a consequence of cognitive impairment and could affect sleep quality and daytime performance.

Several factors suggest that the sleep-cognition relationship works in the opposite direction, i.e., impaired sleep leads to worse cognitive functioning. It has been suggested that poor sleep or sleep loss may be a risk factor for cognitive decline, leading to deterioration of age-related cognitive abilities and could even aggravate or hasten the neurodegenerative processes of AD or other dementia disorders [67;80;81;102;103]. This is supported by data showing that increased Aβ aggregation or fluctuation of Aβ is linked to a disrupted sleep-wake cycle [104], chronic sleep deprivation in rodents [105], and poor or inadequate sleep in cognitively intact older adults [106;107]. Similarly, the sleep process *per se*, plays a restorative role, facilitating the clearance of cellular waste products, including plaque-building proteins that accumulate during wakefulness [108;109].

While sleep is crucial for memory consolidation [110] and optimal cognitive functioning, prolonged sleep loss has the potential to affect hippocampal integrity, thereby leading to cognitive dysfunction [111;112]. Studies have shown that changes in neural networks, in particular glial alterations in the hippocampus, may underpin poor sleep quality and sleep-related cognitive decline, even in healthy older people [108].

Individuals differ significantly in their degree of cognitive vulnerability to sleep loss, so those with preclinical dementia disorders are probably at greater risk of becoming symptomatic, leading to further cognitive decline [103;111].

Considering that sleep disordered breathing is associated with worse cognitive functioning and increased risk of MCI and dementia in elderly people [89;113;114], our findings may at least be partly explained by the persistence of sleep disorders, e.g., sleep apnea related to poor sleep quality. However, participants were not selected on the basis of their having a sleep disorder, and EDS was comparable between the groups, and in all cases was below the cutoff for suspecting EDS-related sleep disorders [44;115]. Polysomnographic data from the present study will be presented elsewhere.

Perhaps the most likely reason for the association between cognitive decline and sleep disturbances is that they have a common underlying origin that affects both the sleep and cognitive systems. Since sleep-wake disturbances and cognitive dysfunction frequently co-occur in neurodegenerative diseases, these processes might be underpinned by disruptions of the common neurobiological circuits [33;116]. One potential factor is that the e4 allele of apolipoprotein E (APOE), or another underlying genetic mechanism, enhances the vulnerability to disturbed cognition and sleep in the same individual. While the presence of the APOE e4 genotype is

considered a major risk factor for cognitive decline and dementia [117-119], it has also been linked to sleep disturbances in rodents [120], OSA [121-123] and an increased risk of physiological [92] but not subjective [86;93] sleep disturbances in MCI patients and the non-demented elderly. Additionally, there may be less thoroughly explored mechanisms linking impaired sleep to cognition, such as neuroinflammation or metabolic dysregulation [124;125]. Chronic insomnia, extremes of habitual sleep duration and age-related sleep alterations are all associated with changes in inflammatory cytokine levels and cortisol [126;127]. Inflammatory changes in the brain are thought to be involved in the pathogenesis of dementia disorders and depression, and to cause increased neurodegeneration and reduced neuroprotection and neuronal repair [128;129].

Yet another possible common factor is subclinical depression, which may predispose to an increased risk of poor sleep and of impaired cognition. Sleep-related symptoms such as insomnia, EDS and fatigue are strongly related to depression, anxiety and an increased risk of future depression and cognitive decline [90;130-133]. Moreover, subclinical depression may moderate the link between sleep quality and cognitive performance [134] and changes in sleep may be associated with increased risk of cognitive decline, as a function of greater depressive symptoms [86]. These findings indicate that depressive symptoms may enhance vulnerability to cognitive decline in subjects with poor sleep, or that poor sleep quality may increase the risk of depressive symptoms, in turn inducing cognitive dysfunction. However, in the present study, the groups were comparable with respect to depressive symptoms, and in all cases below the cutoff for suspected depressive disorders [48]. Therefore, it does not appear likely that subclinical depression was responsible for the differences in quality of sleep. Finally, a decline in sleep quality and cognition may be partially due to the aging process itself. Age-related changes in the structure and function of the brain and weakening of the circadian and homeostatic mechanism may affect sleep pattern and cognitive performance [35;135].

With respect to education, significant differences in education may reflect the effects of educational attainment on midlife cognitive functioning, and to a lesser extent also be a consequence of different trajectories of age-related decline in cognitive functioning. Young adult cognitive ability and educational level are usually highly correlated [41] and evidence suggests that childhood cognitive ability influences the educational level achieved [136]. Education in early adulthood is known to be associated with cognitive abilities in late midlife [137-139], but cognitive ability in young adulthood is more closely associated than education with midlife cognitive ability

[42]. However, greater cognitive abilities in young adults may protect against cognitive decline [140], perhaps reflecting a higher likelihood of participation in adult education and training [138]. Further analyses adjusting for the draft board educational measure showed that group differences in young adult education did not explain midlife group differences in cognition. .The above discussion demonstrates that it is an open issue whether the group differences in sleep quality observed in the current study reflect early signs of cognitive decline, if sleep disorders are a marker, or whether cognitive decline or some other as yet unidentified common factors are responsible for the association.

Our finding that there is no association between self-rated daytime sleepiness or sleep duration and cognition is consistent with the results of previous studies in the community dwelling elderly [69;71] but conflict with those of others [59;62;82;84;85;91]. Our findings support and extend those of previous reports showing that sleep symptoms [83;86;90] or poor sleep quality measured in short-term [80] and long-term [67] follow-up studies may be an early sign of cognitive decline. Similarly, cognitive decline has been associated with subsequent actigraphic sleep disturbances among community-dwelling non-demented older adults [88].

Consistent with previous studies [57;63;64;72;82] we found that sleep quality and longer sleep onset latencies were correlated with current cognitive performance, whereas total sleep duration was not. This indicates that sleep quality is more likely to affect cognitive decline than sleep quantity [72]. However, this contrasts with previous observations in subjects with and without cognitive impairment, no dementia (CIND), who did not differ in terms of PSQI measured sleep quality, sleep latency or duration [95].

Finally, our findings support the common sense notion that older adults in good health ("successful agers") are more likely to have fewer sleep complaints, better sleep quality and greater daytime alertness. [6-11]. Here, mean levels of sleep quality and daytime sleepiness were relatively similar to previously reported values in a community-dwelling sample of middle-aged and older subjects [9;47;133;141-143] and lower than in clinical samples [44;115].

Our study has several strengths. Most notably, it has a longitudinal design, and involves a relatively large sample size of middle-aged males drawn from a well-established, population-based birth cohort, screened for neurological and psychiatric comorbidities, and alcohol and drug abuse. In addition, our study benefits from the use of standardized well-validated sleep questionnaires, and a comprehensive neuropsychological test battery consists of well-validated paper-and-pencil tests and the widely used CANTAB computer-based battery. The latter was

designed to include measures sensitive to subtle cognitive changes in healthy people, and the earliest signs of mild cognitive impairment and dementia. In this sense, our study is superior to previous ones, which used more limited cognitive test batteries. Nevertheless, some limitations should be acknowledged. The Metropolit 1953 Danish Birth Cohort comprises only Caucasian men born in 1953, so our findings may not be applicable to women, other age groups, clinical samples of patients with cognitive impairment, or other ethnicities. To avoid factors confounding the sleep/cognition relationship we excluded subjects with neurological and psychiatric diseases, depression, and who were drug and alcohol abusers. Thus, study participants were probably healthier than the national average and may not be entirely representative of the general population, in which depressive mood and other comorbidities are common and often related to sleep disturbances. However, the descriptive results in our study suggest that the PSQI and ESS reports may be generalized to middle-aged, reasonably healthy men. The low overall response rate in the CEHA study (34%) means that we cannot rule out the possibility of participation bias, which would lead to an underrepresentation of subjects with poorer mental or physical health.

It should be noted that participants in the current study were selected as outliers in late-midlife cognitive tests but did not have a clinical diagnosis of MCI or a preclinical dementia condition. Thus, it is possible that the findings could be attenuated or stronger associations between sleep and cognition could have been observed if assessed in older or more cognitively impaired populations. Since sleep data were collected only once, we cannot determine the habitual sleep pattern over time, or identify causal relationships between sleep and cognition. Moreover, self-report data may be confounded by overall bias. Although free of underlying psychiatric and neurological illnesses, a variety of medical, social or sleep-related conditions or medications could potentially influence sleep reports in our study sample [11;144;145]. We included depression measures but not direct measures of anxiety and stress, and data were restricted to subjective sleep measures, which may be considered a limitation of our study. Higher PSQI scores and less striking EDS [133] are closely related to psychological well-being and distress, depressed mood, anxiety [69;98;143;146], increased use of hypnotics [69], socio-economic status [147;148] and subjective cognitive complaints [69]. Thus, PSQI is perhaps more a measure of negative attitude and dissatisfaction than of physiological sleep quality. Moreover, while work-related distress declines around retirement, a transient increase in subjective sleep quality appears to occur at this time [149;150], suggesting that the decline in subjective sleep quality across the life span is not linear.

It can be argued that our study sample included subjects who will develop MCI or neurodegenerative disease as well as subjects who will remain cognitively healthy. Thus, only a continued prospective follow-up of this cohort can better characterize cognitive trajectories and determine whether individuals with worse sleep quality will ultimately show accelerated cognitive decline, depression or both.

In conclusion, the results of this study suggest that changes in cognition are associated with reduced sleep quality in healthy middle-aged males. Here we provide evidence of a relationship between self-rated poor sleep and cognitive decline, as indicated by the reduced sleep quality of individuals with impaired cognitive functioning. Future prospective and intervention research, including subjective and objective measures of sleep, is needed to confirm this relationship and to clarify the underlying biological mechanisms. Such studies would allow researchers to determine whether poor sleep quality is merely a consequence of cognitive decline, or is a marker of decline, or may actually contribute to or accelerate cognitive decline and the emergence of neurodegenerative disorders. Identifying the preclinical factors related to cognitive decline and acting upon them could have a major public health benefit; if strong precursors related to disturbed sleep can be identified, then we would have potential early disease markers and targets for preventive interventions.

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Table 1. Demographic and clinical data

	Cognitively improved (N = 97)	Cognitively impaired (N = 92)	p
Age (years)	57.87 ± 0.64 (97)	57.98 ± 0.74 (92)	n.s.
Sex, male (%)	100 (97)	100 (92)	n.s.
Caucasian (%)	100 (97)	100 (92)	n.s.
Education (years)	14.10 ± 2.27 (97)	12.43 ± 2.18 (92)	< 0.001
BMI (kg/m^2)	26.40 ± 3.8 (97)	26.98 ± 3.43 (92)	n.s.
Waist circumference (cm)	97 ± 23 (95)	101 ± 18 (84)	n.s.
Blood pressure (mm Hg): Systolic Diastolic	 140 ± 21 (95) 85 ± 13 (95)	 139 ± 20 (88) 87 ± 14 (88)	n.s.
Alcohol drinking habit Current (Yes/No)	 95/2	 89/3	n.s.
Smoking habit Current (%) Former (%)	 28 (29) 40 (41)	 19 (21) 40 (43)	n.s.

Never (%)	29 (30)	33 (36)	
<u>Physical and psychiatric morbidity:</u>			
Hypercholesterolemia	13 (13%)	16 (17%)	n.s.
Hypertension	24 (25%)	27 (29%)	n.s.
Other current or former cardiovascular disease	11 (11%)	9 (10%)	n.s.
Type 2 diabetes	4 (4%)	2 (2%)	n.s.
Asthma/COPD	1 (1%)	3 (2%)	n.s.
Arthritis	14 (14%)	27 (29%)	0.013
Allergic illness	4 (4%)	1 (1%)	n.s.
Gastrointestinal illness	2 (2%)	3 (3%)	n.s.
Any current or former migraine or other neurological disease	17 (18%)	10 (11%)	n.s.
Any former malignancy	2 (2%)	4 (4%)	n.s.
Any former depressive episode	7 (7%)	12 (13%)	n.s.

Data are mean and standard error of the mean, or percentage. n.s. = not significant ($p > 0.05$). Groups were compared using unpaired t-tests (continuous variables) or χ^2 tests (categorical variables).

Table 2. Pharmacological classes most frequently prescribed to the study sample.

ATC group	Cognitively improved (N = 97)	Cognitively impaired (N = 92)	P
Any daily used medication	48 (50%)	64 (70%)	0.005
A. Drugs for ulcer and reflux	3 (3%)	7 (8%)	n.s.
Antidiabetic drugs	3 (3%)	3 (3%)	
B. Antithrombotics	10 (10%)	12 (13%)	n.s.
C. Antihypertensive	20 (11%)	30 (16%)	n.s.
Lipid-lowering agents	13 (13%)	16 (17%)	
M. Musculoskeletal system	1 (1%)	5 (5%)	n.s.
N. Antidepressant, anxiolytic and antiepileptic drugs	0 (0%)	6 (7%)	<0.011
R. Asthma or respiratory disease	2 (2%)	4 (4%)	n.s.
Any other drug	4 (%)	10 (9%)	n.s.
Vitamins/supplements	41 (42%)	33 (36%)	n.s.

Table 3. Comparison of means of BPP, I-S-T 200 R and test scores for the two groups (N = 189).

	Cognitively improved (N = 97)	Cognitively impaired (N = 92)	T	P
BPP test	46.82 (9.54)	45.06 (8.20)	1.36	n.s.
I-S-T200R	43.03 (7.15)	20.95 (6.10)	22.80	< 0.001
Overall test mean	0.56 (0.78)	-0.52 (0.91)	8.75	< 0.001
MMSE/ACE	0.38 (0.80)	-0.36 (0.99)	5.67	< 0.001
TRAILMAKING/SDMT	0.37 (0.82)	-0.42 (1.07)	5.68	< 0.001
15 WORD PAIR	0.42 (0.84)	-0.39 (0.93)	6.30	< 0.001
DMS	0.18 (0.89)	-0.14 (1.06)	2.28	< 0.05
PAL/PRM	0.42 (0.84)	-0.32 (0.99)	5.67	< 0.001
SOC/SRM	0.36 (0.92)	-0.32 (0.94)	5.06	< 0.001
RTI/RVP	0.30 (0.09)	-0.32 (0.10)	4.47	< 0.001

BPP: Børge Priens Prøve; I-S-T200R: Intelligence Structure Test 200R; MMSE: Mini Mental State Examination; ACE: Addenbrooke's Cognitive Examination; SDMT: Symbol Digit Modalities Test; DMS:

Delayed Matching to Sample; PAL: Paired Associates Learning; PRM: Pattern Recognition Memory; SOC: Stockings of Cambridge; SRM: Spatial Recognition Memory; RTI: Reaction Time; RVP: Rapid Visual Information Process

Standard deviations in parentheses.

Table 4: Comparison between groups for subjective sleep and mood characteristics.

	Cognitively improved (N = 97)	Cognitively impaired (N = 92)	p
ESS	6.52 ± 3.19	5.95 ± 3.43	n.s.*
ESS ≥ 10 n (%)	15 (8)	15 (8)	n.s.
PSQI global	4.31 ± 2.32	5.29 ± 3.70	0.03*
PSQI > 5 n (%)	37 (19)	40 (21)	n.s.
Sleep quality (C1)	0.79 ± 0.77	0.91 ± 0.74	n.s.
Sleep latency (C2)	0.67 ± 0.95	0.83 ± 1.06	n.s.
Sleep duration (C3)	0.85 ± 0.63	0.94 ± 0.66	n.s.
Sleep efficiency (C4)	1.39 ± 9.99	0.40 ± 0.82	n.s.
Sleep disturbances (C5)	1.30 ± 0.46	1.20 ± 0.54	n.s.
Medication use (C6)	0.04 ± 0.20	0.16 ± 0.54	n.s.
Daytime dysfunction (C7)	0.71 ± 0.72	0.69 ± 0.53	n.s.
Self-rated total sleep time	6.69 ± 1.00	6.55 ± 1.29	n.s.
Self-rated sleep latency	11.59 ± 7.95	16.80 ± 22.16	n.s.
Daytime napping n (%)	41 (22)	33 (18)	n.s.
BDI-II	3.32 ± 3.79	4.19 ± 5.14	n.s.
BDI-II ≥ 14 (%)	3 (2)	4 (2)	n.s.

ESS, Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index; BDI-II, Beck's Depression Inventory. Mann-Whitney U test** Unpaired t-test*. Values are expressed as mean ± SD or n (%). n.s = not significant ($p \geq 0.05$)

Table 5. Partial correlations (controlled for BPP) between subjective sleep variables and cognitive variables (N=189)

	Global PSQI	ESS	Sleep latency	Sleep durationn	BDI
I-S-T2000R					
Overall test mean	-0.19**	0.06	-0.30**	0.00	-0.08
MMSE/ACE	-0.19**	0.12	-0.28**	0.00	-0.10
TRAILMAKING/SDMT	-0.14	0.06	-0.20**	-0.02	0.03
15 WORD PAIR	-0.02	-0.03	0.01	-0.11	-0.10
DMS	-0.14	0.08	-0.22*	0.06	0.03
PAL/PLM	-0.13	0.01	-0.21*	0.15	-0.12
SOC/SRM	-0.10	0.00	-0.16*	0.00	-0.08
RTI/RVP	-0.03	-0.06	-0.14*	-0.04	-0.05

PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale; BDI: Becks Depression Inventory ; MMSE: Mini Mental State Examination; ACE: Addenbrooke's Cognitive Examination; DMS: Delayed Matching to Sample; PAL: Paired Associates Learning; PRM: Pattern Recognition Memory; SOC: Stockings of Cambridge; SRM: Spatial Recognition Memory; RTI: Reaction Time; RVP: Rapid Visual Information Process

p<0,05* p<0.01**, NS; non significant.